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Pillsbury Winthrop LLP
Intellectual Property Group
Suite 200
11682 El Camino Real.
San Diego, CA 92130-2092

| EXAMINER | |
|---|---|
| KOLKER, DANIEL E | |
| **ART UNIT** | **PAPER NUMBER** |
| 1649 | |

DATE MAILED: 07/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/731,411 | COX ET AL. | |
| | Examiner | Art Unit | |
| | Daniel Kolker | 1649 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *31 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1, 5 - 42* is/are pending in the application.

4a) Of the above claim(s) *14-18 and 25-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-13 and 19-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1, 5-42* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Applicant's remarks, amendments, and declaration filed 31 May 2005 have been entered in full. Claims 2 – 4 and 44 – 76 have been cancelled. Claims 1 and 5 – 43 are pending in the instant office action.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Claim Objections*

3. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

There is no claim number 27. Misnumbered claims 28 - 43 have been renumbered 27 – 42. All references to claim numbers in this Office action are to the new numbering scheme.

### *Election/Restrictions*

4. Applicant's confirmation of the election of Group I and Alzheimer's in the reply filed on 31 May 2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

5. Applicant's election with traverse of brain tissue as the specific tissue in the reply filed on 31 May 2005 is acknowledged. The traversal is on the ground(s) that BMAA can be measured in brain tissue and in skin samples. This is not found persuasive because:

MPEP 808.01(a) states:

> Election of species should be required prior to a search on the merits (A) in all applications containing claims to a plurality of species with no generic claims, and (B) in all applications containing both species claims and generic or Markush claims. In all applications in which no species claims are present and a generic claim recites such a multiplicity of species that an unduly extensive and burdensome search is required, a requirement for an election of species should be made prior to a search of the generic claim. (emphasis added)

In the instant case, there are generic claims (claims 1, 22, and 27) as well as claims containing species (claims 24 – 26 and 28 – 42), namely specific tissues to be tested. The claims are analogous to (B) in the quotation from MPEP above.

Applicant argues that because BMAA can also be detected in hair, as shown in the declaration filed by Dr. Branack, the requirement for election of species should be withdrawn. The declaration under 37 CFR 1.132 filed 31 May 2005 is insufficient to overcome the election of species set forth in the last Office action because: it does not address the question of whether distinct non-obvious species were claimed. The declaration presents data from hair samples, and correlates the level of BMAA in hair with the presence of dementia. This is not germane to the election of species, as the election of species requirement was made not on the basis of whether or not BMAA could be detected in non-neurological tissue, but whether multiple specific embodiments of a generic claim were claimed. Multiple genera and sub-genera of tissues were claimed, and in each case specific embodiments were claimed.

The requirement is still deemed proper and is therefore made FINAL.

6. Claims 14 – 18 and 25 – 42 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 31 May 2005.

7. Claims 1, 5 – 13, and 19 – 24 are pending and under examination.

***Withdrawn Rejections and Objections***

8. The following rejections or objections made in a previous office action are hereby withdrawn:

The rejections of claims 5 and 6 under 35 USC 112, second paragraph. On p. 8 of the remarks applicant points out that the specification defined the term "protein bound BMAA" as including both BMAA incorporated into protein and otherwise bound to protein. The term is broad but is not indefinite.

The rejections of claims 1, 2, 7 – 13, 22, and 23 under 35 USC 102(b) for being anticipated by Ellison and Martinez, and of claim 24 for being anticipated by Ellison. The prior art teachings are drawn to glutamate; applicant has amended the claims to recite BMAA rendering the rejections moot.

***Claim Rejections - 35 USC § 112***

9. Claims 1, 5 – 13 and 19 - 24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detection of BMAA in patients with Alzheimer's disease or ALS-PDC, does not reasonably provide detection of BMAA in other neurological disorders, or for predicting the likelihood of developing, or severity of, or latency period to developing the disorder. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

On page 7 of the remarks, applicant argues that the specification is enabling for detection of BMAA in patients with Alzheimer's disease and ALS-PDC. Applicant refers to the declaration filed under 1.132 by Dr. Banack and the accompanying table, as well as to Table 3 of the specification, as offering support. Applicant's arguments are convincing to the extent they are limited to methods of detecting BMAA in patients known to have ALS-PDC and Alzheimer's disease. In the previous office action, the examiner stated that the specification was enabling for screening subjects for the presence of BMAA wherein the BMAA is associated with Alzheimer's disease. The examiner did not reject claim 12, drawn to ALS-PDC or claim 13, drawn to Alzheimer's, under the scope of enablement rejection. The specification is enabling for detecting BMAA in patients having both these diseases.

The claims are drawn to methods of screening subjects having or at risk of having a neurological disorder. The specification (p. 5) defines screening as including "diagnosing or predicting neurological disorders". The specification does not provide sufficient guidance to allow a skilled artisan to predict whether or not a patient has a neurological disorder in all patients who either have or are at risk of having a neurological disorder. All people are at risk of having neurological disorders, including Alzheimer's disease (see Cassel et al., 2001, cited in previous office action, particularly Figure 4.3 and Table 4.1, both on p. 36), even those who never develop the disease. The specification does not enable screening as defined by applicant. This term includes prediction, and the only data provided by applicant are retrospective. To be fully enabled, the specification would have to provide enablement for the prediction of Alzheimer's disease, including in those who are asymptomatic (see claim 8). Clearly the post-mortem brain tissue samples from table 3 of the specification do not provide predictive value. Furthermore the data presented in the declaration submitted under 1.132 are insufficient to overcome the rejection under 35 USC 112. The data presented do not permit

prediction of neurological disorders. The data in Exhibit 2 are also retrospective. In fact, all asymptomatic patients had undetectable levels of BMAA.

Applicant argues, on p. 7 of the remarks, that pp. 12 – 14 of the specification provide sufficient guidance for the artisan to be able to predict the likelihood of developing a neurological disease (claim 19), the latency to the onset of the disorder (claim 20), and the severity of the disorder (claim 21). Applicant's arguments have been considered but are not deemed persuasive. The data presented in the specification and declaration clearly do not enable one of skill in the art to predict the likelihood of developing neurological diseases. On page 13, second paragraph of the specification applicant discloses that BMAA is elevated in a person who is asymptomatic at the time of death (see also Table 3). Clearly detecting elevated levels of BMAA is not sufficient to determine the likelihood of developing the disease, the severity of the disease, or the latency to onset of the disease, because it can be detected at relatively high levels in the brain of an asymptomatic person. The data presented in Exhibit 2 of the 1.132 declaration also indicate that BMAA levels are not well-correlated with the severity of the disease. Patients with a clinical diagnosis of Alzheimer's disease had BMAA levels (ug/g hair) ranging from 4.0 – 44.4. Those with Alzheimer's type dementia had levels ranging from 9.8 – 47.4. The single patient with Pre-Alzheimer's vascular dementia had 32.3 ug BMAA per gram of tissue, and the single patient with Dementia had 10.1. The ranges overlap to such a large degree that it is impossible to predict the severity of the disease given the BMAA level.

Applicant also argues that the data presented in Table 3 of the specification and Exhibit 2 of the declaration permit the prediction of the latency until onset of the disease and the likelihood of developing disease. The examiner disagrees. Neither the specification nor the declaration provides any data on the latency until the onset of disease, or the probability of developing a disease. The data presented in Exhibit 2 indicate that asymptomatic people have no BMAA in their hair, but does not show any data on latency to onset of disease, as all people with detectable levels of BMAA already had received a clinical diagnosis of dementia or Alzheimer's disease. Furthermore there are no data either in the specification or the declaration relating to the likelihood, which would be expressed by relative risk or a similar measure, of developing diseases.

For the reasons made of record and reiterated above, claims 1, 5 – 13 and 19 – 24 are not deemed enabled over their full scope and stand rejected under 35 USC 112, first paragraph.

***Claim Rejections - 35 USC § 102***

10. Claims 1, 7 – 13, and 22 – 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Kisby. Kisby teaches a method of detecting BMAA in tissue samples from subjects having or at risk of having neurological disorders wherein BMAA is associated with the neurological disorder. Kisby teaches detection of of BMAA in serum from monkeys that were treated with BMAA (see page 46, column 2, and page 47 "Sample preparation for HPLC" and "BMAA and amino acid analysis"). Kisby also teaches that administration of BMAA induces extrapyramidal symptoms in monkeys and mice (p. 45 second column) and that exposure to BMAA "has been suggested as an etiologcal trigger of amyotrophic lateral sclerosis/Parkinsonian dementia complex". Clearly the monkeys used in Kisby's experiments were at risk of developing neurological diseases in general and ALS-PDC in particular, as the monkeys were exposed to BMAA and Kisby teaches this induces neurological changes and is a risk factor for ALS-PDC. Thus the reference explicitly meets the limitations of claims 1, 9, 11, and 12.

Applicant's arguments filed 31 May have been fully considered but they are not persuasive. Applicant argues, on pp. 9 – 11 of the remarks, that there are important differences between ALS-PDC and Alzheimer's disease, and that while there appears to be contemplation of the use of the method in detecting or diagnosing ALS-PDC, claim 13 was improperly rejected.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., having Alzheimer's disease) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claim 1 recites "a subject having or at risk of having a neurological disorder". Claim 13 ultimately depends from claim 1 and recites "wherein the neurological disorder is Alzheimer's disease." The claims are not drawn to methods of detecting BMAA in patients with Alzheimer's disease, but rather are drawn to analyzing tissue samples to determine the presence of BMAA in subjects having or at risk of having Alzheimer's disease. As set forth on p. 9 of the previous office action, all people are at risk of having Alzheimer's disease. Kisby explicitly contemplated the use of his method on people. He mentioned in the abstract and in the first paragraph of the paper the importance of BMAA in ALS-PDC, which is a disease that effects people. Since Kisby taught the claimed method, contemplated its use on samples from people, and all people are at

risk of having Alzheimer's disease, Kisby fairly teaches the limitations of claims 1, 9, and 11 – 13.

Kisby also teaches that repeated oral administration of BMAA induces extrapyramidal symptoms in primates (p. 45 second column, referring to a paper by Spencer et al., Science 237:517-522, cited in previous office action), and teaches that the monkeys used in the study were subjected to 12 months of daily oral administration of BMAA (see p. 46, second column). Kisby did not report that the subjects had symptoms of a neurological disorder, but the teachings of Spencer, on which Kisby relied to design his experiments, clearly indicate that treatment with BMAA produces symptoms of neurological disease within 2 – 12 weeks (Spencer, p. 518, first column). Thus Kisby fairly teaches detection of BMAA in subjects with symptoms of neurological disease, meeting the limitation of claim 7. Kisby also teaches screening tissue to determine the presence of BMAA in tissue from control animals (see paragraph spanning pp. 51 – 52), fairly meeting the limitation of claim 8, drawn to asymptomatic subjects. Kisby also fairly teaches that the presence of BMAA indicates neurological disorders, as the reference discloses that BMAA can be detected in monkeys treated with BMAA for a year but not in control animals, and thus meets the limitations of claim 10. Kisby teaches detecting BMAA in rat brain tissue, meeting the limitation of claims 22 – 24.

***Claim Rejections - 35 USC § 103***

11. Claims 1, 5, and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kisby et al., in view of Duncan et al. (1990, reference LR from the Information Disclosure Statement filed April 12, 2004) and Duncan et al. (1992). In the previous office action claim 1 was not included in this rejection due to a typographical error. However because claims 5 and 6 were rejected, and they depend from claim 1, the base claim should have been included in the grounds of rejection. The examiner does not believe this constitutes a new grounds of rejection. The claims are drawn to methods of screening samples to determine the presence of BMAA (claim 1), wherein protein-bound BMAA is analyzed (claim 5) and where free BMAA is also analyzed (claim 6).

Applicant argues, in the middle of p. 12 of the remarks, that the combination of references does not teach analysis of protein-bound BMAA as claimed herein. Applicant has defined "protein-bound BMAA" on page 10, lines 13 – 22 of the specification as including "incorporated into a protein or it may be otherwise associated with a protein." This is a very broad definition. The broadest reasonable interpretation of "otherwise associated with a protein"

includes being associated with proteins by acid-labile bonds. As set forth in the previous office action, Duncan (1992) teaches a method of analyzing total BMAA from cycad flour and refers the reader to the earlier (1990) publication. Duncan (1990) teaches the hydrolysis of BMAA-containing proteinaceous samples with hydrochloric acid for 36 hours (p. 768, right column). The specification of the instant application teaches the hydrolysis of BMAA-containing proteinaceous samples for 24 hours (p. 38) in hydrolchloric acid. Both methods are sufficient to release very high levels of BMAA from samples. Duncan quite clearly teaches the same method to release BMAA from protein samples that applicant uses, namely incubation with hydrochloric acid. The examiner is not convinced of applicant's argument that Duncan does not teach analysis of protein-bound BMAA because Duncan uses the same method as applicant to release BMAA that has been bound to protein.

Applicant also argues, in the paragraph spanning pp. 12 – 13 of the remarks, that the rejection relies on an improper interpretation of the term 'protein bound BMAA'. First, it is noted that the term 'protein-bound BMAA' has been defined very broadly by applicant on p. 10 of the specification and it includes BMAA that is "otherwise associated with a protein". Applicant argues that the burden is on the examiner to provide evidence for the assertion that proteins can be broken down into their constituent amino acids by hydrolysis. The examiner provides herein pages from the textbook Molecular Biology of the Cell by Alberts et al. (1994, Third Edition). Alberts clearly states that "peptide bonds can be hydrolyzed in the absence of an enzyme by exposing a polypeptide to either a strong acid or a strong base" (Alberts, p. 132), and that proteins are made of amino acids joined together by peptide bonds (Alberts, p. 56, see panel in the middle of the page). One of ordinary skill in the art would clearly recognize that HCl, which is a strong acid, would dissolve a protein into its constituent amino acids by hydrolysis. MPEP 2144.03, which applicant has cited on p. 13 of the remarks, states "It would not be appropriate for the examiner to take official notice of facts without citing a prior art reference where the facts asserted to be well known are not capable of instant and unquestionable demonstration as being well-known." The examiner believes that it was appropriate to rely on a textbook published nine years before the provisional application was filed without citing said textbook in the first office action, but has done so here for applicant's convenience and to make the record complete.

In the first complete paragraph on p. 13 of the remarks applicant argues that the differences in the methods used by Duncan and by applicant are sufficient to overcome the

rejection. The examiner disagrees. Duncan subjected the samples to 0.1 M HCl for 72 hours. One of ordinary skill in the art would know that HCl is a strong acid, and that 0.1 M HCl has a pH of 1.0. Alberts provides the definition of pH on p. 49. Given the definition of "protein bound BMAA" provided by applicant, the facts about protein chemistry that are provided herein, and the teachings of Duncan, the examiner asserts it would have been obvious to one of ordinary skill in the art to combine the teachings of Duncan with those of Kisby, with a reasonable expectation of success. A motivation to do so would be to allow detection of all the BMAA in the sample, thereby being better able to correlate the level of BMAA with the presence or risk of acquiring a disease. It would be reasonable to expect success because one of ordinary skill in the art would have known that proteins are made of amino acids held together by peptide bonds, that peptide bonds are acid labile, and that in order to detect all of an amino acid in a sample it would be prudent to release that amino acid from the peptides into which it is incorporated or otherwise associated. Thus the rejection of claims 1, 5, and 6 under 35 USC 103 is maintained.

***Conclusion***

12. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel E. Kolker, Ph.D.
July 26, 2005

BRENDA BRUMBACK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600